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CENTRAL INTELLIGENCE AGENCY
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INFORMATION REPORT

REPORT

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COUNTRY	USSR	DATE DISTR.	24 [illegible] 1949
SUBJECT	Toxicology	NO. OF PAGES	4
PLACE ACQUIRED	USSR	NO. OF ENCLS. (LISTED BELOW)	
DATE OF INFORMATION	September 1947	SUPPLEMENT TO REPORT NO.	

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THIS IS UNEVALUATED INFORMATION FOR THE RESEARCH USE OF TRAINED INTELLIGENCE ANALYSTS

SOURCE Russian periodical, Byulleten Eksperimental'noy Biologii i Meditsiny, Vol XXIV, No 3, 1947, "Pathogenesis of Botulism, IV: Reaction of Vascular Tissues of Humans and Animals to Botulismotoxin." (~~FDB Per Abs 29T77~~ -- Translation specifically requested.)

REACTION OF VASCULAR TISSUES OF HUMANS AND ANIMALS TO BOTULISMOTOXIN

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(Submitted to the editor, 8 March 1947)

The mechanism of botulin intoxication in humans and animals is still not clear, in spite of a considerable amount of work which has been done on the subject (Dack, Dack and Hoskins, Wood, Fridman and Lorber, Shleynberg, Dutaygin and Khayfets, Petrovskiy, Naumenko and Baturenko, Serebryannaya and Shkavera, and others).

Results of experimental research conducted to determine the accuracy of the hypothesis of clinicians on the vascular contractive action of botulismotoxin and presented in the present work.

Experiments with vessels of human kidneys, rabbit ears, and the hind half of guinea pigs were carried out according to the Kravkov-Pisemskiy method, which uses pure toxin. The use of such a toxin produced more definite results concerning the reaction of the vessels.

A dry toxin of type A or B botulism bacilli was prepared by precipitation in an ammonium sulphate solution. The toxin floating on the surface of the medium was collected in a cup and carefully pressed to remove moisture. Then the toxin was dried, pulverized into fine powder in a mortar, and titrated to determine its virulence.

A toxin of considerable toxicity was used in the experiments; 0.000001 to 0.0000001 g was lethal for mice. The dry toxin was diluted 100 times

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and then subjected to dialysis through a collodion bag for 16 - 18 hours in running tap water, and then for 24 hours in distilled water.

With this method it was possible to obtain a toxin free from the many impurities which are found in a liquid toxin. The toxin which we obtained contained almost no amines which did not precipitate in ammonium sulphate solution. In addition, it was freed from some albumins in the medium which had not precipitated in the concentrated ammonium sulphate solution. With dialysis, several impurities of various salts and possibly many other substances were removed.

After dialysis the toxicity of the solution decreased 2 - 3 times. Apparently, this was due to partial destruction and dissipation of the toxin during dialysis. Accordingly, solutions with high toxicity were used in the experiments.

Experiments with the ears of 15 rabbits were carried out in the first series. Previously, the artery in the ears of the rabbits was separated and tied with two ligatures. Then the ear was incised with a sharp razor between the two ligatures. The vessels of the ear were washed with a warm Ringer-Locke solution. When their constant tone was established, which was determined by the quantity of liquid discharged in one minute, we introduced first a weak and then a stronger concentration of the toxin. The first toxin dilution was 1:50,000; the second was 1:25,000; and the third was 1:10,000.

The ordinary solution of the toxin was introduced in one ear of 6 rabbits of this series, and a solution of attenuated toxin into the others. A toxin dilution of 100 times was attenuated by heating in a water bath after dialysis for 15 - 20 minutes.

The vessels in the ears of all 15 rabbits reacted to the botulismotoxin and contracted (see table).

The vessels had an average contraction of 23.2 percent with the first dilution, 36.5 percent with the second dilution, and 36.9 percent with the third. The vessels of the rabbit ears reacted almost identically to the second and third dilution of the toxin.

Vessels of the ears of the 6 rabbits, through which the attenuated toxin had been introduced, had an insignificant contraction. The average contraction with the first dilution was 4 percent, and with the second and third dilutions, 6 and 6.5 percent.

Very definite results of the reaction of the vessels in the rabbit ears to botulismotoxin were obtained in these experiments: the higher the concentration of the toxin, the stronger the contraction of the vessels. Botulismotoxin which had been attenuated by heating, then purified by preliminary sedimentation and subjected to dialysis, caused a very slight contraction of the vessels in the rabbit ears, especially in comparison with natural toxin.

Reaction of Blood Vessels of Animals and Humans to Botulismotoxin

Exp ser	Type of vessel	Experiment: No of exp	Experiment: Av decrease of drops in passage of diluted toxin (%) 1:50,000	1:25,000	1:10,000	Control: No of exp	Control: Av decrease of drops in passage of diluted toxin (%) 1:50,000	1:25,000	1:10,000
1	Rabbit Ears	15	23.2	36.5	36.9	6	4	6	6.5
2	Guinea Pigs	10	23.1	25.2	35.8	5	4.6	6.4	3.8
3	Human Kidneys	10	22.1	25.5	32.7	3	4.9	7.4	16.7

The second series of experiments was with 15 guinea pigs (see table).

The guinea pigs were killed with a blow on the head. The abdominal cavity was opened, the abdominal aorta tied off with a ligature, and then the guinea pigs cut in half with sharp scissors. A glass cannula was inserted into the aorta of the hind half of the guinea pigs and the veins irrigated with a warm Ringer-Locke solution. After this the preparation was examined on a slide and again a Ringer-Locke solution was put through until a point was reached where a constant volume of liquid flowed out per minute.

Identical dilutions of toxin as in the previous series were studied here. The reaction of vessels of 10 guinea pigs were tested with a toxin which had not been heated. Due to the passing of the first and second dilutions of the toxin, the vessels of the animals had an average contraction of 23.1 - 25.2 percent, and with the third dilution, 35.8 percent. Toxin which had been attenuated by heating caused a contraction of vessels of 5 guinea pigs of 4.2 - 6.4 percent.

The results of the experiments with guinea pig vessels did not differ from the results of experiments of the first series, which were made with rabbit ear vessels. The guinea pig vessels reacted with a considerable contraction to the botulismotoxin and showed almost no reaction to the toxin which had been attenuated by heating.

The reaction of vessels of human kidneys to botulismotoxin was studied in the third series.

In order to obtain definite results, it was very important to use fresh organs from persons not suffering from vascular disease, which was determined by autopsy. We succeeded in getting organs for the most part within 4 - 6 hours after death.

6 A total of 13 experiments were made with kidneys. The method was the same as in previous experiments. A glass cannula was introduced into the artery of the kidney and a warm Ringer-Locke solution run through it until the solution contained no blood. After this a solution of botulismotoxin of the same series and the same dilution as used in the previous experiments was run through the vessels of the kidney.

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With the first dilution of the toxin, the vessels of ten human kidneys had an average contraction of 22.1 percent; with the second, 25.5 percent; and with the third, 32.7 percent. Contraction of vessels of three kidneys due to the passing of heated toxin was 5.7 percent with the first dilution, 7.4 percent with the second, and 16.5 percent with the third. The results of the experiments with human kidneys were the same as the results of the previous experiments (see table).

Thus, the vessels of rabbit ears, the hind half of guinea pigs, and the human kidney reacted identically to botuliamotixin. The contraction of these organs was distinguished only by the intensity.

The strongest contractions were indicated in the vessels of the rabbit ears and the weakest in the vessels of the human kidney. The weakest contraction of vessels was on the average 22 percent, and the strongest was 37 percent. A toxin which had been attenuated by heating in a water bath caused a very weak reaction of the vessels in animals.

It seems to us that these experimental studies gave complete confirmation of the observations of clinicians on the condition of the cardiovascular system in botulism. An increased pulsation with a weaker heart tone, paleness of the skin, and dryness of mucous membranes were observed in patients. Clinicians have offered the hypothesis that this comes about in connection with the vascular contractive action of botuliamotoxin. This hypothesis was confirmed in our experiments.

Consequently, clinical observations and experimental research have confirmed the fact that botuliamotoxin is a strong vascular poison which causes the contraction of the vessels in humans and animals.

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